Remarks

In the Office Action, the Examiner noted that claims 1-3, 6-12, 15-22 and 25-28 are pending in the application; claims 4, 5, 13, 14, 23 and 24 are withdrawn from consideration; and that claims 1-3, 6-12, 15-22 and 25-28 are rejected. By this amendment, claims 21, 22, 27 and 28 have been amended, and claims 1-18, 23 and 24 have been cancelled without prejudice or disclaimer of the subject matter contained therein. Thus, claims 19-22 and 25-28 are pending in the application.

No new subject matter has been inserted through these amendments. All of the amendments are fully supported by the specification. Specifically, claim 21 has been amended to replace the word "quadrisaccharide" with tetrasaccharide." Also, claim 21 was amended to delete the phrase "or a physiologically functional derivative thereof." Claim 22 was amended to provide a missing period at the end of the claim. Claim 27 was amended to provide an expansion for the terms, HMG-CoA and APP. Support for the expansion of the notation HMG-CoA can be found in the specification at page 3, line 12. Similarly, support for the expansion of the notation APP can be found in the specification at line 5, page 2. Finally, claim 28 was amended to properly depend upon method claim 27 as it inadvertently recited as depending upon a composition claim. In view of the above amendments to claim 21 pertinent parts of the specification has also been amended by deleting two occurrences of the word "quadrisaccharide" and inserting therefor "tetrasaccharide." The Examiner's rejections are respectfully traversed below.

Election/Restriction

In making previously imposed two-way restriction final in this case, the Examiner has withdrawn claims 4, 5, 13, 14, 23 and 24. As a result, by way of this amendment Applicants have canceled claims 4, 5, 13, 14, 23 and 24 without prejudice or disclaimer of the subject matter contained therein. Further, Applicants reserve the right to place the canceled subject matter in one or more divisional applications.

Claim Objections under 37 CFR 1.75(c)

Claim 9 stands objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim.

However, claim 9 has been canceled without prejudice obviating this objection. Accordingly, withdrawal of this objection as to claim 9 is respectfully requested.

Claims 2, 11 and 21 stand objected to because of the fact that the Examiner has pointed out that the recited term, "quadrisaccharide" in these claims be replaced with more accepted term "tetrasaccharide." Again, as noted above, as the claims 2 and 11 have been canceled without prejudice this objection is rendered moot as to these two claims. However, claim 21 has been amended as suggested by the Examiner. Thus, withdrawal of objection as to claims 2, 11 and 21 is respectfully requested.

Double Patenting Rejection

Claims 1-3, 8-12, 15, 17-18 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,019,023; claims 1-3 of U.S. Patent No. 6,642,269; claims 1-7, 9-15 of U.S. Patent No. 6,387,944; claims 1-5, 11-12, 19-21, 23, 25, 27 and 29 of U.S. Patent No. 6,221,897; and claim 1 of U.S. Patent No. 6,107,494.

However, as noted above, claims 1-3, 8-12, 15, 17-18 have been canceled without prejudice obviating this rejection. Thus, withdrawal of rejection as to claims 1-3, 8-12, 15, 17-18 is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 6-12, 15-22 and 25-28 stand rejected under 35 U.S.C. 112, first paragraph, because the Examiner alleges that the specification while being enabling for treating Alzheimer's disease using the compounds of formula IA and for compositions comprising compounds of formula IA and statins (HMG-CoA reductase inhibitors) and

ezetimibe (cholesterol reductase inhibitor), does not reasonably provide enablement for the said treatment using a combination of the compound of formula IA and all other inhibitors that fall under the broad categories recited in claim 27 and also does not provide enablement for the compositions comprising a combination of the compound of formula IA and all other inhibitors that fall under the broad categories as recited in claims 8-9.

Again, as noted above, since claims 1-3, 6-12, 15-18 have been canceled without prejudice this rejection is rendered moot for these claims. Thus, the only relevant claim for which this rejection applies is claims 27, which recites basically a combination of compounds of this invention (i.e., BARI, including compounds of formula IA) and the following four classes of inhibitors:

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors,

cholesterol uptake inhibitors,

cholesterol synthesis inhibitors, or

γ and β amyloid-β precursor protein (APP) secretase inhibitors.

As further noted above, the Examiner has already acknowledged the presence of enablement for two of these inhibitors, namely, statins (HMG-CoA reductase inhibitors) and ezetimibe (cholesterol absorption or uptake inhibitor). Thus, the Examiner is objecting only to the other two classes of inhibitors recited in claim 27, which are: cholesterol synthesis inhibitors and γ and β APP secretase inhibitors. However, the sate of the art is such that one of skilled in the art readily appreciates using a combination of compounds of formula IA and a cholesterol synthesis inhibitor or a γ and β APP secretase inhibitor for treating Alzheimer's disease following the teachings of the instant invention as recited in claim 27 without resorting to undue experimentation at the time Applicants made this invention. Accordingly, it is respectfully submitted that claim 27 satisfies the requirements of 35 USC 112, 1st paragraph.

In support of Applicants' assertion, the Examiner's attention is respectfully drawn to the article by Josien H., Curr, Opin. Drug Discov. Develop. 2002, 5(4), 513-25. As stated therein:

> Alzheimer's disease is a neurodegenerative disorder that exerts a huge psychological and social toll in modern societies. The current hypothesis for the cause of this illness is that it is the result of aberrant production of beta-amyloid (A beta) and plaque deposition in the brain of affected individuals. New therapeutic interventions seek to stop or even reverse the course of the disease by inhibiting this aggregation or reducing A beta formation. *The use of inhibitors of gamma-secretase, a key enzyme in the production of A beta, is currently undergoing preclinical and clinical evaluation. Small molecule inhibitors which demonstrate efficacy in reducing A beta burden in mice have thus been recently discovered.* (emphasis added, see abstract of Josien H. review)

From the above it is clear that there is enough evidence in the literature that γ and β APP secretase inhibitors are useful in treating Alzheimer's disease.

Similarly, there have been numerous studies linking the cholesterol with Alzheimer's disease. Again, the Examiner's attention is particularly drawn to the passages in the specification beginning at page 2, line 18 to page 3, line 4 and numerous references cited therein. In addition, the biological examples provided at page 13 to 16 further support the use of a combination of compounds of formula IA with a cholesterol synthesis inhibitor. The Examiner's attention is particularly drawn to FIGs. 1 to 4 where the results of such studies are shown. In view of the foregoing, it is respectfully submitted that only remaining claim that may be subject to this rejection meets the criteria for 35 USC 112, 1st paragraph, i.e., claim 27 is fully enabled based on the teachings in the specification and in light of the state of the art as described hereinabove. Accordingly, withdrawal of rejection as to claims 1-3, 6-12, 15-22 and 25-28 is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 2-3, 8-12, 15-18, 21-22 and 27-28 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner has noted that claims 2, 11 and 21 recite the terms "physiologically functional derivatives," which are not fully described in the specification. As noted, claims 2 and 11 have been canceled without prejudice. Further, claim 21 has been amended to delete the above noted phrase, thus obviating this rejection.

The Examiner has noted that claims 3, 12 and 22 do not end in a period. Again, claims 3 and 12 have been canceled without prejudice and claim 22 has been amended by providing a period, thus obviating this rejection.

The Examiner has further pointed out that claims 8, 17 and 27 recite notations HMG-CoA and APP and requesting to provide expansions to these terms. Claim 27 has been amended as requested and claims 8 and 17 have been canceled without prejudice, thus obviating this rejection.

The Examiner alleges that claim 9 recites the limitations "separately or spaced out" in claim 8, and states that there is insufficient antecedent basis for this limitation. However, claims 8 and 9 have been canceled without prejudice. But the Examiner states that similar recitation is seen in claims 18, 27 and 28. Claim 18 is also canceled rendering this rejection moot. As to claims 27 and 28, it is respectfully submitted that claim 27 is a method claim and claim 28 which depend directly upon claim 27 provides an additional limitation of administering the combination either "simultaneously, separately or spaced out over time." Thus, withdrawal of rejection as to claims 27 and 28 is respectfully requested.

Finally, claim 10 has been rejected as being indefinite, but claim 10 has been canceled rendering this rejection moot.

In view of all of the foregoing arguments and reasoning it is respectfully requested that the rejection as to claims 2-3, 8-12, 15-18, 21-22 and 27-28 under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-3, 6-12 and 15-18 stand rejected under 35 USC 102(b) as being anticipated by Frick et al (US 6,221,897).

However, as noted above, claims 1-3, 6-12 and 15-18 have been canceled without prejudice rendering this rejection moot. Accordingly withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 8-12 and 15-18 stand rejected under 35 USC 103(a) as being unpatentable over Frick et al (US 6,221,897) and Castaner et al (Drugs of the Future, 2000, 25(7), 679-685).

However, as noted above, claims 8-12 and 15-18 have been canceled without prejudice rendering this rejection moot. Accordingly withdrawal of this rejection is respectfully requested.

Claims 18-22 and 25-28 stand rejected under 35 USC 103(a) as being unpatentable over Frick et al (US 6,221,897) in combination with Refolo et al (Neurobiology of Diseases, 2001, 8, 890-899).

Claim 18 has been canceled without prejudice obviating this rejection as to claim 18.

However, contrary to the views of the Examiner, it is respectfully submitted that claims 19-22 and 25-28 are patentably distinguishable from Frick et al in combination with Refolo et al, and therefore fully satisfy the requirements of 35 USC 103(a). Accordingly, withdrawal of rejection as to claims 18-22 and 25-28 is respectfully requested.

More specifically, as properly stated by the Examiner, Frick et al disclose compounds of formula IA. However, Frick et al neither teach nor suggest that the compounds of formula IA are useful for the treatment of Alzheimer's disease, as also explicitly acknowledged by the Examiner (see page 13 of the Office Action). Thus, Frick et al do not provide any motivation to one skilled in the art of medicinal chemistry to arrive at the instant invention at the time Applicants made this invention.

In addition, Refolo et al disclose that cholesterol could play a major role in the pathogenesis of Alzheimer's, but do not teach the use of compounds of formula (Ia) for treating Alzheimer's as presently taught in the instant invention. Refolo et al describe that statins and more generally, compounds that inhibit HMG-CoA reductase can be used for treating Alzheimer's disease (page 897,last paragraph), but do not mention compounds of formula IA. Moreover, Refolo et al use a compound, BM15.766, which is reported to be blood-brain barrier permeable (page 892, right column, last paragraph). However, the compounds of formula IA of this invention are not believed to be blood-brain barrier permeable. In fact the compounds of formula IA do not penetrate into the body after its oral administration. See page 4, lines 17 to 23 of the specification. As specifically stated therein:

> "Surprisingly, it has therefore been demonstrated that the biliary acid reuptake inhibitors (BARI) are effective in an animal model of Alzheimer's disease *by acting only through the regulation of the plasma cholesterol level and in particular by not penetrating into the brain, because they are not absorbed in the body*. (emphasis added)

Please also see specific recitation of such a limitation in claim 19: "does not penetrate into the body after its oral administration." Thus, it is submitted that Refolo et al not only

fails to teach or suggest that a compounds of this invention can be used to treat Alzheimer's, but in fact it teaches away from the present invention. In view of this, it is submitted that there is no teaching, suggestion or motivation from the teachings of Frick et al in combination with Refolo et al to arrive at the present invention at the time Applicants made this invention.

For all of the arguments advanced above, it is respectfully submitted that claims 19-22 and 25-28 are non-obvious over Frick et al in combination with Refolo et al. Accordingly, withdrawal of this rejection is respectfully requested.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 19-22 and 25-28 are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

Applicants believe there are no fees due for this Rule 111 Amendment. However, if the Examiner deems that fees are due, please charge these fees to Deposit Account No. **18-1982** for sanofi-aventis U.S. LLC, Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

January 2, 2007

Respectfully submitted,

Balaram Gupta

Balaram Gupta, Ph. D., J. D.
Registration No. 40,009
Attorney for Applicants

sanofi-aventis U.S. LLC
US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626